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Association of Systemic Medication Exposure With Glaucoma Progression and Glaucoma Suspect Conversion in the Groningen Longitudinal Glaucoma Study

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Purpose. To determine the association of statins, five classes of antihypertensive medications, and proton pump inhibitors with (1) primary open-angle glaucoma (POAG) progression and (2) conversion of POAG suspects to POAG.

Methods. We retrospectively investigated the records of a cohort with POAG cases and suspects from the Groningen Longitudinal Glaucoma Study. To quantify visual field (VF) deterioration in cases, we used the rate of progression of the mean deviation (MD). Suspects were considered to have converted at the time point after which two consecutive VF tests for at least one eye were abnormal (glaucoma hemifield test outside normal limits). Progression and conversion were analyzed with quantile and logistic regression, respectively, with the systemic medications as predictors, controlling for age, sex, body mass index, pretreatment IOP, corneal thickness, and baseline MD. The multivariable models were built with and without IOP intervention.

Results. No systemic medications were associated with POAG progression in the final IOP/treatment-adjusted or unadjusted model. However, angiotensin II receptor blockers (ARBs) appeared to slow progression in older patients (b = 0.014, $P = 0.0001$). Angiotensin-converting enzyme inhibitors (ACEIs) were significantly associated with a decrease in POAG suspect conversion in both the IOP/treatment-adjusted and -unadjusted model (odds ratio [OR] 0.23, 95% confidence interval [CI] 0.07–0.79, $P = 0.012$; OR=0.24, 95% CI 0.07–0.78, $P = 0.021$, respectively), as were ARBs (OR 0.12, 95% CI 0.01–0.98, $P = 0.014$; OR 0.11, 95% CI 0.01–0.87, $P = 0.005$, respectively).

Conclusions. No overall association of VF progression with systemic medication was found; ARBs delayed progression in older patients. ACEIs and ARBs were associated with lower risk of suspect conversion. The pathophysiology of this relationship is to be disentangled.

Keywords: glaucoma, ocular hypertension, antihypertensives, statins, proton pump inhibitors

Glaucoma is a chronic and progressive eye disease characterized by cupping of the optic disc, thinning of the retinal nerve fiber layer, loss of retinal ganglion cells (RGCs), and loss of visual function.[1,2] A high IOP is an important risk factor for glaucoma and IOP-lowering medications, laser, or surgery are currently the only available options to delay, but not inhibit, glaucomatous progression.[3,4] However, not every person with ocular hypertension will convert to the disease, and glaucoma also may develop in those with an apparently normal IOP.[5] These observations imply that other risk factors exist that are not being addressed in current treatment decisions.

Several other factors may contribute to the development and progression of the disease, including systemic medications used to treat other pathologies. Specifically, a protective role of statins, possibly unrelated to their cholesterol-lowering effect, has been reported in primary open-angle glaucoma (POAG).[6–9] Moreover, numerous studies have examined the effect of antihypertensive (AH) medication on glaucoma, because the disease is believed to contain a vascular component.[10–12] This suggests that drugs able to modify vascular events could pertain to the outcome of glaucoma. In this regard, proton pump inhibitors (PPIs), a medication class used to lower the levels of stomach acid in gastric and esophageal pathologies, could influence unfavorably the course of the disease because of their documented inhibition of nitric oxide (NO) production.[13] To make it even more complicated, these drugs could simultaneously have a beneficial effect because they create an unfavorable gastric environment for *Helicobacter pylori*, a bacterium for which an association with increased risk for POAG has been suggested.[14]

However, the results of studies examining the role of statins and AH medication in POAG are conflicting.[15,16] A neuroprotective property of statins as well as of certain AH medications has been suggested, but not all studies confirm such an effect.[17,18] Even from a pathophysiological perspective, although hypertension has been suggested as a risk factor for glaucoma, aggressive treatment with blood pressure (BP) medication also could result in ischemic damage to the RGCs mediated by a low diastolic BP.[19] In addition, to the best

of our knowledge, there currently exists only scarce evidence addressing a potential effect of PPIs on POAG development. Last, some study designs in the literature incorporate a loose definition of POAG (e.g., prescription of glaucoma medication) based on national registries or insurance claim data.[11,16] As a result, it is impossible to differentiate the impact of systemic medication on glaucoma suspects from the corresponding impact on those with a glaucoma diagnosis.

Therefore, the aim of this study was to determine the association of statins, five main classes of AH medication, and PPIs with (1) POAG progression and (2) conversion of POAG suspects to a POAG diagnosis. For this purpose, we retrospectively looked into the information of the Groningen Longitudinal Glaucoma Study (GLGS) to determine exposure to the aforementioned systemic medications in a cohort of POAG patients and POAG suspects.

Methods

Study Population

Patients were selected from the GLGS database. The GLGS began in 2000 and was originally a prospective, observational cohort study conducted in the clinical setting of the University Medical Center Groningen (UMCG), comprising both glaucoma patients and glaucoma suspects (predominantly Caucasians). In 2000, the UMCG served both as an academic and as a community hospital; most patients in the current study should be considered community hospital patients. The objectives and methods of the GLGS have been previously described.[20,21] After the onset of the original GLGS, we continued adding newly diagnosed glaucoma patients, making the GLGS a dynamic population. From those patients who visited the clinic in 2015, we recorded their current and past systemic medications, and height and weight. This is the subset used in the current study. For the glaucoma patients, we associated the rate of progression (ROP; defined below) with systemic medication use, making the study design a retrospective follow-up study. For glaucoma suspects, we compared systemic medication use between those who converted to glaucoma and those who did not, making the study design a case-control study. The study protocol was approved by the ethics board of the UMCG and followed the tenets of the Declaration of Helsinki. All patients provided written informed consent.

To be eligible, subjects had to be followed with standard automated perimetry (see next subsection). Those with pseudoexfoliative or pigment dispersion glaucoma or a history of angle closure or secondary glaucoma were excluded (leaving POAG and POAG suspects). For being a glaucoma patient, glaucomatous visual field (VF) loss had to be present at baseline in at least one eye.[20] For glaucomatous baseline VF loss, two consecutive tests had to be abnormal (see next subsection) in at least one eye. Defects had to be compatible with glaucoma and without any other explanation. A VF test before the two baseline tests was discarded to reduce the influence of learning. Thus, at least three tests had to be performed at baseline before glaucomatous VF loss could be diagnosed. Glaucoma suspects were those who had an intact VF when entering the study and were followed in our outpatient department because of ocular hypertension (IOP above 20 mm Hg on at least two separate visits), a positive family history of glaucoma (glaucoma reported in father, mother, brother, or sister), or a suspected optic disc (cup-to-disk ratio above 0.6), or combinations thereof.[22]

Perimetry, Progression, and Conversion

Perimetry was performed using the Humphrey Field Analyzer (Carl Zeiss, Jena, Germany) 30–2 Swedish interactive threshold algorithm fast strategy with 30–2 grid. An abnormal test result was defined as a glaucoma hemifield test "outside normal limits." Test results were included only if they were reliable; a test result was considered unreliable if false positives exceeded 10% or if both false negatives and fixation losses exceeded 10% and 20%, respectively. We pooled false negatives and fixation losses because they were reported to have a much smaller influence on the mean deviation (MD) and the false negatives, especially, are not informative in glaucoma.[23,24]

In glaucoma patients, the ROP was calculated as the slope of the MD over time, after a minimum of 5 years of perimetric follow-up.[25] For the conversion analysis, subjects who were glaucoma suspects were considered to have converted to a glaucoma diagnosis at the time point after which all subsequent VF tests (at least two) for at least one eye were abnormal.

Risk Factors

The possible risk factors for glaucoma progression that were included in this study were age at baseline, sex, body mass index (BMI), highest pretreatment IOP, central corneal thickness (CCT), baseline MD (dichotomized above and below the median of –9.4 dB),[26] mean IOP during follow-up, surgery for glaucoma (yes/no), number of glaucoma medications, and systemic medications. Systemic medications included were statins, diuretics, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), beta blockers, and PPIs. For the number of glaucoma medications, topical and oral were included, and if the patient underwent laser treatment, this was considered as an additional medication.[27]

Systemic Medication Exposure Ascertainment

To verify systemic medication exposure, the complete medical file of each patient was examined, in combination with a semi-structured interview that took place in 2015 (at or toward the end of the follow-up). An interviewer (blinded to the study question and taking no other part in the study procedures) asked each participant to list his or her current medications, guiding them with additional questions, such as: "What medications are you currently taking for high blood pressure/high cholesterol/your heart/your stomach?" To ascertain prior or subsequent use of the reported or other relevant medications, we recorded all medication listings until the end of the patient's follow-up from the patient's hospital file, which included letters to his or her primary care doctors detailing prescribed medications. We defined the 'oldest recorded exposure date' as the very first date a drug appeared in this listing (or mentioned in the interview), while being absent from all listings of previous reports. We used this date (1) to approximate the duration of systemic medication use during follow-up for the progression analysis and (2) to ascertain that systemic medication exposure occurred before the conversion date in the conversion analysis.

Data Analysis

For the progression analysis, only one eye per patient was included. If a patient met the inclusion criteria with both eyes, a randomly chosen eye was included. Conversion was based on a by-patient basis: those who converted with at least one eye were considered to have converted; for analysis, the first

Table 1. Demographics of the Study Population

	Glaucoma Patients	Glaucoma Suspects	
		Converted	Not Converted
Number of patients	250	53	59
Age at baseline, y; mean ± SD	61.8 ± 9.9	58.3 ± 10.0	55.4 ± 11.3
Sex, % female	46.0	56.6	54.2
BMI, kg/m^2; mean ± SD	26.2 ± 4.2	25.6 ± 3.8	27.2 ± 4.5
IOP before treatment, mm Hg; median (IQR)	26.0 (22.0 to 31.0)	26.0 (23.0 to 30.0)	29.0 (24.0 to 32.0)
CCT, μm; median (IQR)	537.0 (512.5 to 566.0)	543.0 (519.0 to 558.0)	551.0 (539.5 to 576.0)
VF MD at baseline, dB; median (IQR)	−9.4 (−15.6 to −5.1)	−1.1 (−3.9 to 0.0)	−0.8 (−1.8 to 0.2)
Follow-up duration, y; median (IQR)	12.0 (9.0 to 15.0)	7.0 (4.0 to 12.0)	16.0 (13.0 to 18.0)
Mean IOP during follow-up, mm Hg; median (IQR)	13.2 (11.3 to 15.5)	15.5 (13.9 to 17.3)	17.1 (14.6 to 18.2)
ROP, dB/y; median (IQR)	−0.27 (−0.55 to −0.08)	NA	NA
Statins, % (*n*)	37.2 (93)	15.1 (8)	40.7 (24)
Statin duration, percentage of follow-up years; median (IQR)	45.6 (25.3 to 82.5)	NA	NA
Diuretics, % (*n*)	27.6 (69)	9.4 (5)	33.9 (20)
ARBs, % (*n*)	15.2 (38)	1.9 (1)	15.2 (9)
ACE inhibitors, % (*n*)	24.8 (62)	7.5 (4)	25.4 (15)
CCBs, % (*n*)	19.2 (48)	11.3 (6)	20.3 (12)
Beta blockers, % (*n*)	27.2 (68)	18.8 (10)	30.5 (18)
AH duration, percentage of follow-up y; median (IQR)	50.0 (27.3 to 100.0)	NA	NA
PPIs, % (*n*)	33.2 (83)	22.6 (12)	32.2 (19)
PPI duration, percentage of follow-up y; median (IQR)	44.4 (25.8 to 90.4)	NA	NA

NA, not applicable; VF MD, standard automated perimetry mean deviation.

converted eye was used and if no conversion took place, a random eye was chosen. The patient characteristics were described with mean and SD for normally distributed variables. For variables with a skewed distribution, we used median and interquartile range (IQR) instead. In the multivariable analysis (see below), missing data for CCT (2 cases) and BMI (3 cases) were imputed from the median value. There were no other missing values for any other risk factor.

Because of the non-normality of the ROP distribution, quantile regression was performed using a saturated model with ROP as the outcome variable and all predictor variables included. The least significant variable was then removed, and the models with and without the least significant variable were compared using the Akaike information criterion (AIC). If the model without the concerning variable was the better fit for the data, the same process was repeated for the next least significant variable, and this process was continued until we reached a minimal model. Coefficients and *P* values were reported. The saturated model for the ROP regression can be found in the supplementary material (Supplementary Table S1).

Conversion of glaucoma suspects to a glaucoma diagnosis was analyzed using a logistic regression model. The saturated model included all the predictor variables included above, except for glaucoma surgery and baseline MD, which would both be irrelevant for those not yet diagnosed with glaucoma. Mean IOP during follow-up was calculated either until the point at which the patient converted, or for the entire follow-up duration if the patient never converted. Again using the AIC, covariates were removed and a minimal model was created. Odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values were reported. The saturated model for the conversion logistic regression model can be found in the supplementary material (Supplementary Table S2).

All analyses were performed using R (version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria). A *P* value of 0.05 or less was considered statistically significant. According to the AIC, inclusion in the final model implies $P < 0.16$.

Results

We included 250 patients in the ROP analysis and 112 glaucoma suspects for the conversion analysis. Of the 112 glaucoma suspects, 21 were included because of ocular hypertension, 4 because of a positive family history of glaucoma, 6 because of a suspected optic disc, and 81 because of combinations thereof. Table 1 shows the characteristics of the study population.

Median follow-up duration of the glaucoma patients was 12 years; median ROP −0.27 dB per year. Table 2 depicts the univariable quantile regression analysis with median ROP as the dependent variable. Older age, lower BMI, lower IOP before treatment, and a higher number of glaucoma medications were significantly associated with faster progression.

Table 3 shows the final multivariable model for median ROP, along with a model built without the variables that account for

Table 2. Univariable Quantile Regression Analysis for Glaucoma Patients With Median ROP as Dependent Variable

	Coefficient	*P* Value
Age, y	−0.006	0.003
Sex, female	0.080	0.15
BMI, kg/m^2	0.010	0.050
IOP before treatment, mm Hg	0.005	0.008
CCT, μm	−0.0002	0.76
VF MD at baseline, dB	0.000	1.0
Mean IOP during follow-up, mm Hg	−0.005	0.52
Glaucoma surgery, 0 = No	0.040	0.44
Number of glaucoma medications	−0.046	0.028
Statins	−0.060	0.27
Diuretics	−0.010	0.87
ARBs	0.020	0.74
ACE inhibitors	−0.060	0.23
CCBs	−0.080	0.31
Beta blockers	−0.080	0.16
PPIs	0.010	0.86

Table 3. Final Models for Glaucoma Patients With Median ROP as Dependent Variable

	Final Model		Final Model (Not Adjusted for IOP Intervention)	
	Coefficient	*P* Value	Coefficient	*P* Value
Age, y	−0.007	0.001	−0.006	0.010
Sex, female	0.122	0.018	0.128	0.004
BMI, kg/m^2	0.010	0.032	0.006	0.14
IOP before treatment, mm Hg	0.004	0.12	0.004	0.077
CCT, µm	−0.0008	0.14	−0.0007	0.16
Number of glaucoma medications	−0.036	0.056	NA	NA
Statins	−0.083	0.086	NA	NA
ARBs	0.089	0.097	NA	NA

intervention by the treating ophthalmologist (by excluding mean IOP during follow-up, number of glaucoma medications, and glaucoma surgery from the saturated model) to account for any systemic medication-mediated IOP changes. In both final models, older age and male sex were significantly associated with faster progression. Specifically, for each 10 years of age, the median ROP was 0.07 dB per year faster (0.06 dB per year for the model excluding intervention). Statins and ARBs remained in the model but were not significantly associated with ROP.

For these two systemic medications, we completed a secondary dose-response relationship analysis in which we created categories based on duration of medication use, defined as follows: no use, duration of use below the median, and duration of use above the median. Compared with nonusers of statins, there was a trend toward faster progression with prolonged statin use (6 years or less, b = –0.083, $P = 0.06$; more than 6 years, b = –0.130, $P = 0.009$). There was no dose-response relationship found for ARBs.

We also repeated the analysis using a variable with the cumulative number of AHs (in place of the different classes) as a marker for the severity of hypertension, but this variable was the first to leave the model, suggesting the number of AHs was not associated with progression.

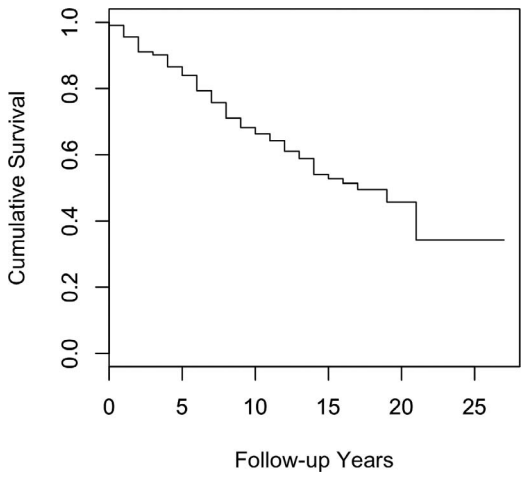

Figure. Survival curve for the glaucoma suspect population. Conversion to POAG is defined as the time point after which all subsequent VF tests (at least two) for at least one eye were abnormal.

Table 4. Univariable Analysis With Glaucoma Suspect Conversion as Dependent Variable

	OR (95% CI)	*P* Value
Age, y	1.03 (0.99–1.06)	0.14
Sex, female	1.1 (0.52–2.32)	0.80
BMI, kg/m^2	0.91 (0.83–1.00)	0.043
IOP before treatment, mm Hg	0.98 (0.94–1.03)	0.44
CCT, µm	0.99 (0.98–1.00)	0.058
Mean IOP during follow-up, mm Hg	0.90 (0.80–1.01)	0.078
Number of glaucoma medications	0.53 (0.34–0.85)	0.004
Statins	0.26 (0.1–0.65)	0.002
Diuretics	0.20 (0.07–0.59)	0.001
ARBs	0.11 (0.01–0.87)	0.008
ACE inhibitors	0.24 (0.07–0.78)	0.009
CCBs	0.50 (0.17–1.44)	0.19
Beta blockers	0.53 (0.22–1.28)	0.15
PPIs	0.62 (0.26–1.43)	0.26

Interactions between the two systemic medications remaining in the final model (ARBs and statins) and both pretreatment IOP and age also were investigated, with a Bonferroni-adjusted significance cutoff of $P = 0.0125$. The only significant interaction effect on ROP was between ARBs and age (b = 0.014, $P = 0.0001$). For each additional 10 years of age, ARB takers had a median ROP that was 0.14 dB per year slower than non–ARB takers. In addition, tests for collinearity between systemic medications revealed only a moderate collinear relationship between beta blockers and ACEIs (phi = 0.42, $P < 0.001$), all other phi coefficients were similar or lower.

Of the 112 glaucoma suspects, 53 converted during follow-up. The median follow-up duration until conversion was 7 years for those who converted; those who did not convert were followed for a median of 16 years. The survival curve is displayed in the Figure. From this curve, it can be predicted that it will take 15 years for 50% of the suspects to convert. Tables 4 and 5 present the univariable and final multivariable logistic regression models, respectively, for glaucoma suspect conversion. In the univariable analysis, a higher BMI, a higher number of glaucoma medications, and the use of statins, diuretics, ARBs, and ACEI were associated with a significant decrease in conversion. Again, multivariable models were built with and without mean IOP during follow-up and number of glaucoma medications. In the final model, a higher number of glaucoma medications and the use of ARBs and ACEI were associated with a significant decrease in conversion to a glaucoma diagnosis. Even in the final model without mean IOP and IOP treatment, the rate of conversion of suspects on ARBs

Table 5. Final Models With Glaucoma Suspect Conversion as Dependent Variable

	Final Model		Final Model (Not Adjusted for IOP Intervention)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y	NA	NA	1.03 (0.99–1.07)	0.14
BMI, kg/m^2	NA	NA	0.93 (0.83–1.07)	0.15
CCT, µm	0.99 (0.98–1.00)	0.063	0.99 (0.98–1.00)	0.069
Number of glaucoma medications	0.59 (0.37–0.94)	0.025	NA	NA
ARBs	0.12 (0.01–0.98)	0.014	0.11 (0.01–0.87)	0.005
ACE inhibitors	0.23 (0.07–0.79)	0.012	0.24 (0.07–0.78)	0.021

and ACEIs was 89% and 76% lower, respectively, than those not taking the drugs, suggesting the possible protective association is not mediated by IOP. Tests for collinearity between systemic medications revealed a moderate collinear relationship between beta blockers and CCBs (phi = 0.53, $P < 0.001$), all other phi coefficients were similar or lower.

Discussion

No systemic medications were associated with POAG progression in the final IOP-intervention adjusted or unadjusted model; statins and ARBs remained in the final IOP-intervention adjusted model without reaching significance, but an interaction term revealed a significantly slower progression associated with ARBs for older ages. ACEIs and ARBs were significantly associated with a decrease in POAG suspect conversion in the final model, regardless of IOP-intervention adjustment.

Regarding the effect of statins on POAG progression, other studies have given varying results. Iskedjian et al.[12] reported no significant differences in the need for adjunct topical IOP-lowering medications between statin users and nonusers. Leung et al.[8] found that significantly more nonprogressors were using statins. In contrast to our study, their study concerned only normal tension glaucoma (NTG) subjects (256 subjects followed for 3 years; 31 taking statins). An interaction term between statin use and pretreatment IOP added to our model did not uncover a significant association, suggesting that statins do not have a selective association with NTG in our study population. De Castro et al.[28] assessed progression with structural parameters and reported that statin users, albeit only those not receiving aspirin treatment simultaneously, had lower progression rates ($n = 76$; smallest group $n = 12$; follow-up duration: 5.5 years). This observation suggests that early structural changes might be more sensitive to the effect of statins compared with VF parameters, but a study assessing both structure and function would be needed to clarify this hypothesis. McCann et al.[15] could not perform a meta-analysis on these studies because the definitions of glaucoma differed. Last, a propensity score analysis by Whigham et al.[6] reported that a history of statin use resulted in slower VF progression (847 subjects followed for 3.5 years; 629 taking statins). However, their propensity score was limited to age, sex, baseline glaucomatous severity, and systemic medical conditions; hence, it did not include some important variables present in our analysis, especially the variables related to IOP. Notably, in our study, the relevant ROP coefficient for the IOP-intervention adjusted model suggests a faster progression (–0.083 dB per year for statin users compared with nonusers), but this result did not reach significance ($P = 0.086$). Our secondary dose-response analysis suggested faster progression for POAG patients using statins for more than 6 years (–0.130 dB per year compared with nonusers, $P = 0.009$), but according to a recent publication this is more likely a result of higher serum cholesterol.[29] All these studies, including ours, were observational studies; that is, the statins were not prescribed as part of a randomized controlled trial (RCT).

With regard to statin use and POAG incidence, most observational studies, but not all, agree that short-term statin use (2 years or less) does not significantly affect the risk.[7,16,30–33] Among them, Stein et al.[7] also examined the conversion of glaucoma suspects ($n = 49.628$) within a retrospective longitudinal cohort design. They found that POAG suspects who used statins for 1 or 2 years had a smaller hazard for conversion (hazard ratio [HR] 0.907, 95% CI 0.846–0.973), but not for the need for glaucoma surgery.[7] It is possible, of course, that any beneficial effect is only a result of longer exposure to the medication.[7,30,32] Interestingly, a large observational prospective study by Talwar et al.[9] (25,420 subjects; 15,898 taking statins) showed reduced POAG incident risk after 2 years of statin use (HR 0.79, 95% CI 0.66–0.96), independent of the cholesterol-lowering effect, dosage, and statin type. It has been suggested that this effect may be mediated by neuroprotective mechanisms.[17,34,35] Albeit significant in these studies with very large sample sizes, the effect sizes were actually small. This illustrates that a visible effect size in large samples does not immediately imply clinical relevance. Notably, in the univariate analysis of our study, statins are shown to be associated (after Bonferroni correction) with a reduced odds ratio for suspect conversion (OR 0.26, 95% CI 0.1–0.65, P[adjusted] = 0.014); however, the multivariate model reveals that this association is mediated by concomitant use of AH medications.

A recent observational study from insurance claim data suggested a causal, protective effect of AH medication, especially those in the renin-angiotensin category, with respect to incident glaucoma.[11] Hirooka et al.[36] reported a similar finding in an NTG sample treated with ACEIs, whereas Yang et al.[18] found a neuroprotective effect of ARBs in a rat model. The authors hypothesized that the decrease in angiotensin II levels reduces the activity of the NADPH-dependent oxidase complex, thus reducing oxidative stress and the subsequent RGC apoptosis. They also discussed that the increase in plasma bradykinin caused by the ACEIs offers extra possibilities: improved blood flow through activation of the L-arginine NO pathway, or protection from glutamate-induced neurotoxicity. In our study, ACEIs and ARBs were significantly associated with lower odds of suspects converting to POAG, which is in agreement with these results. In addition, the highly significant interaction term between age and ARBs in our progression analysis suggests that the older the glaucomatous patient, the more they could benefit from an ARB, as far as their glaucomatous progression is concerned.

The effects of other AH medications are less clear. Beta blockers have been associated with decreased POAG incidence in some studies, whereas the opposite has been reported for CCBs and, sometimes, even ARBs.[16,37,38] Diuretics were associated with increased conversion risk of ocular hypertensives in the European Glaucoma Prevention Study and increased risk of POAG in other studies.[31,38,39] A protective effect of the cumulative number of AH drugs was reported by Horwitz et al.[11]; in addition, Iskedjian et al.[12] showed that the use of AH medication reduced the need for adjunct topical IOP-lowering medication. Overall, these results suggest that AH medication classes might contribute differently to the course of glaucoma; this points toward the fact that pathways other than the BP-lowering effect could be involved.[40,41] Protection could be mediated by an IOP-lowering effect[42–46]; additional neuroprotective mechanisms have been attributed to medication in the renin-angiotensin category, as discussed in the previous paragraph.[47–49]

There are several reasons for these conflicting results. POAG treatment is a dynamic procedure in which the clinician's decisions interfere with the true (untreated) disease progression. Therefore, explanatory variables, such as mean IOP during follow-up or number of glaucoma medications, could mediate or antagonize effects observed in other studies. Furthermore, a threshold effect could exist for certain AH drugs, or a ceiling effect with no further increase in risk for glaucomatous damage after this ceiling has been reached, hampering consistent dose-response findings.[16,37] Last, it is possible that AH treatment is beneficial only when started timely and harmful if started after many years of untreated hypertension. This, however, is impossible to address in an observational study with limited information regarding the time course of BP and its treatment. Interestingly, overtreat-

ment of hypertension leading to hypotension has been reported as a risk factor for glaucoma.[19,50] Noticeably, data extracted from a large cohort study (LifeLines Biobank) reveal that aggressive AH treatment is hardly the case in our region, the northern Netherlands.[51] Indeed, average (SD) systolic BP/diastolic BP values for users and nonusers of AH medication are, within Lifelines, 135(17)/79(10) and 128(15)/76(9), respectively.

PPIs appear to both mitigate and worsen glaucoma. In a study investigating systemic medication use and glaucoma in insurance claims data,[16] it was found that esomeprazole (a PPI), reduced the risk of POAG. This finding was of borderline significance, but the authors hypothesized that it could be due to a reduction in *Helicobacter pylori* rates, and therefore reduced risk of POAG.[14,52] However, PPIs also can decrease production of NO, a vasodilator that plays a role in IOP regulation. POAG patients may already have a genetic and dietary susceptibility to reduced NO bioavailability.[53] In this regard, PPIs may be beneficial to those who do not have alterations in genes responsible for NO production, and harmful to those who do.

This study is limited by its retrospective design and its relatively small sample size. For medication ascertainment, our primary metric was "any use during follow-up" (a commonly used metric in pharmacoepidemiology), but we added duration of use information for the progression analysis and temporal information for the conversion analysis (by ascertaining that systemic medication exposure occurred before the conversion date). Obviously, this metric is still limited by the absence of dosage information. Furthermore, we did not have BP measurements, and for this reason we could not perform a mediation analysis for BP. Instead, we used the number of BP medications as a crude proxy of disease severity. In spite of that, it is true that monotherapy is the traditional initial therapy for hypertension and subsequent medications are added depending on BP target and disease severity. The absence of BP measurements also did not allow us to examine overtreatment of hypertension, a situation that could lead to underperfusion of the RGCs and, hence, mask any protective effects. Nevertheless, our positive findings remain somewhat robust to this limitation, as they all lie on the protective side, whereas overtreatment is expected to have a negative effect on glaucoma progression or conversion. In addition, our population was predominantly Caucasian, so our results cannot be safely generalized, especially because of differential responses to cardiovascular agents among patients of different genetic ancestries. Last, our population's median age leans toward the younger side with regard to glaucoma populations, a limitation that we tried to address by assessing the interactions between systemic medication exposure and age in the models.

The main strength of this study is the long follow-up duration of the population. Furthermore, POAG patients and suspects were defined according to strict criteria, rather than being based on data from national registry or insurance claims. This ensures that the two groups are not cross-contaminated and that no other type of glaucoma is present in the dataset. Moreover, a novelty of this study is controlling the analysis for glaucoma medications, the surgical profile of each participant (operated/not operated), and mean IOP during follow-up. We believe that this reflects reality better, as it simulates the dynamic context of clinicians intervening in the process by trying to slow the glaucomatous progression.

Our study suggests that, within a glaucoma or glaucoma suspect population with regular follow-ups and well-controlled IOP, there exists some extra benefit added by BP medication, but its clinical relevance is unclear. A better study design and a larger sample size are both needed to strengthen these findings. Also interesting from a clinical perspective, a high pretreatment IOP is paradoxically almost beneficial on ROP (stays in the final model, but does not reach significance), whereas most studies show the opposite effect or no effect whatsoever.[26,54,55] This finding indicates that, in this population, the alarm of a higher baseline IOP could have resulted in early diagnosis and efficient, possibly more aggressive, treatment. As such, it is a marker of clinician's responsiveness that is visible due to the observational study design rather than a disease property.

In this study, approximately 47% of glaucoma suspects converted to glaucoma within a median follow-up of 16 years. According to the Ocular Hypertension Treatment Study (OHTS), the expected percentage of converted cases within 5 years is 5% to 10%, so, assuming a linear relation, fewer than 30% of our suspects should have converted.[56] A possible explanation for this discrepancy could be because a healthy optic disc at baseline was additionally required in the OHTS; we also included suspects based on a suspected optic disc (47 of 112). In addition, a positive family history was present in 44% of the participants in OHTS, to be compared with 58% in our study.[57] Together, these differences suggest that our participants were already "further down the line" at baseline. Also, the OHTS used a stricter criterion for conversion (three consecutive abnormal last VF tests, rather than two); however, all of the converted suspects in our study actually had three consecutive abnormal last VF tests, as well. It also must be noted that 6 of 59 nonconverted suspects in our study had (only) one abnormal last VF, but this was not enough to classify them as "converted," because most of these cases are expected to yield a healthy VF on their next visit.[58] Our converters fulfilled the functional criteria of the OHTS, but we did not have data to also include the structural criteria of the OHTS. As such, the difference in conversion rate between both studies is larger than reported above.

In conclusion, we found no overall significant association of glaucomatous VF progression with systemic medication exposure, but ARBs appeared to significantly delay progression in older patients. ACEIs and ARBs were significantly associated with a lower risk of suspect conversion to POAG. Because this study was limited by its design, further investigations, ideally RCTs, are needed to examine these relationships; should they be proven true, their exact pathophysiology is yet to be disentangled.

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